

REMARKS

Claims 1, 3-11 and 16-18 currently appear in this application. The Office Action of June 13, 2006, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Objections

The abstract of the disclosure is objected to because it has not been presented in the proper domestic form.

Submitted herewith is a substitute abstract of the disclosure.

The disclosure is objected to because page 1 of the specification fails to set forth priority to PCT/JP/03/00203.

The present amendment submits this information to be added to the specification.

Rejections under 35 U.S.C. 112

Claims 3-7 and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that "X" in "X-hydrate" has not been defined.

This rejection is respectfully traversed. The term "X" has been deleted from the claims. The variable "X" in claims 3, 4, 6, 7, 17 and 18 is that of the Crystal form D X-hydrate. The variable "X" recited in claims 12-15 is that of Crystal form G X-hydrate. As to the Crystal form D X-hydrate, the value of X has been estimated to be in the neighborhood of $\frac{1}{2}$. However, an accurate value has not as yet been obtained. As to Crystal form G X-hydrate, there are as yet no data capable of determining the value of "X."

It is respectfully submitted that there is no new matter in deleting "X" from the claims because the compounds are defined by their 2-theta angle positions in X-ray diffraction patterns.

Claims 4-7 and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for omitting essential steps. The claims are said to fail to set forth what "treating" the starting product means.

This rejection is respectfully traversed. Claims 4-17 and 16-18 have been amended to recite "conditioning" or "drying under reduced pressure." "Conditioning" is defined in the specification as filed at page 3, lines 7-9, as storing the crystal in a humidifying room or spraying it with humidifying steam.

Art Rejections

Claims 1-18 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as being obvious over Koga et al. European Patent 0 643 068, Miura et al., European Patent 0 846 697 or Miura et al. U.S. 5,959,088.

This rejection is respectfully traversed. Claim 1 relates to Crystal form F. Crystal form F is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 6.6° and 8.5°. Koga discloses Crystal form A and a process for preparing the same. While Crystal form A is hydrated, the Crystal form F is anhydrous. In other words, Koga does not disclose or suggest Crystal form F.

The two Miura patents disclose Crystal form D and a process for preparing the same. However, the Crystal form D in Koga is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 7.1°, 13.5° and 14.2°. These angles were calculated based on Figure 3 of the two Miura patents. It should be noted that the term "Form B" in Figure 2 of Miura'697 and Miura'088 is a clerical error which should be corrected to "Form C." It should also be noted that the term "Form C" in Figure 3 of the Miura patents is a clerical error that should be corrected to "Form D." It is emphasized that the corresponding PCT application, WO97/06177

correctly states "Form C" in Figure 2 and "Form D" in Figure 3.

As explained above, the Crystal form F as claimed herein differs from the Crystal form D of the Miura patents in that both have different 2-theta angle positions in the powder X-ray diffraction patterns. Thus, the compound of claim 1 is neither anticipated by nor rendered obvious by either Miura patent.

Furthermore, the Crystal form F is useful as an intermediate of Crystal form D hydrate, which is superior in terms of stability and residual solvent to the crystal forms disclosed in Koga or either Miura patent.

The stability and residual solvent of Crystal form D hydrate will be explained below.

With regard to claim 3, Koga discloses a process for preparing a hydrate of Crystal form A in Example 57. While the melting point of Crystal form A is 135-137°C (page 35), the melting point of Crystal form D hydrate of claim 3 is 200°C. Thus, it is clear that Crystal form D hydrate is different from Crystal form A. Therefore, claim 3 is neither anticipated nor obvious over Koga. Miura et al.'697 and Miura et al.'088 disclose Crystal form D and a process for preparing the same. However, since the Crystal form D of the Miura patents is not a hydrate, it is not the same as the hydrate

claimed herein. There is nothing in either Miura patent that suggests producing as hydrate of Crystal form D.

Attached hereto are copies of reference materials Fig. 1-(i), Figure 1-(ii), figure 2 and Table 1. The DSC (differential scanning calorimetry) charts of the Crystal form D disclosed in the Miura patents are shown in Figure 1(i) and 1-(ii). The DSC chart of the Crystal form D anhydrate of the present invention is shown in Figure 2. A declaration is currently being prepared to present these data in proper declaration form, which declaration will be submitted as soon as possible.

According to these charts, it can readily be seen that while a trace amount of Crystal form C (refer to the portion of the endothermic peak at about 381°C in Figure 1-(ii)) remains in the Crystal form D disclosed in the Miura patents. However, the amount of Crystal form C is below the limit of detection in the Crystal form D anhydrate of claim 3. These charts demonstrate that the Crystal form D anhydrate as claimed herein has greater purity than the Crystal form D of the prior art. Therefore, it can be said that the Crystal form D anhydrate as claimed herein has a higher melting point than the Crystal form D of the cited art, and that, therefore, the herein claimed Crystal form D anhydrate is thermodynamically more stable than those of the cited patents.

In addition, Table 1, which relates to data on the residual solvent of each of the Crystal form D anhydrates as claimed herein, and the Crystal form D of the cited patents, shows that the residual solvent in the herein claimed Crystals is much lower than that of the cited patents.

On the other hand, the comparative data shown in Tables 1, 2 and 3 on pages 25-27 of the present specification show that the Crystal form D hydrate as claimed herein is superior to the Crystal form D anhydrate in stability and residual solvent. Therefore, the Crystal form D hydrate is unexpectedly superior to the Crystal form D of the cited patents in both stability and residual solvent.

In addition, both Miura patents state that the Crystal form D is more stable than the Crystal form A (please see page 17, Example 11 of Miura'697 and column 20, Example 11, of Miura'088). Thus, the Crystal form D hydrate, which is more stable than the Crystal form D in the cited patents, is more stable than the Crystal form A. Therefore, it is respectfully submitted that the Crystal form D hydrate is neither the same nor obvious over Crystal form A.

The process for preparing the Crystal form D hydrate as claimed herein is different from the process used by Koga et al. and the Miura et al. patents. The process described in Miura'697 can be found at page 8, compound VII, and the

process described in Miura'088 can be found at column 7, lines 21-68 and column 8, lines 1-23. These patents state that the Crystal form D is purified by recrystallizing a crude crystal of a fumarate of a compound of formula (II) from an alcoholic solvent and performing another recrystallization from hydrous ethyl acetate. Both patents teach that the molar ratio of the Crystal form D to fumaric acid is 2:1.

In addition, the Miura patents disclose that Crystal form A is purified by recrystallization of the compound of formula (VII) with a mixture of methanol and isopropanol, and that Crystal form D is obtained by recrystallization of the thus obtained Crystal form A with a mixture of ethyl acetate and water (please see page 14 of Miura'697 and column 15 of Miura'088).

In contrast thereto, the Crystal form D hydrate as claimed herein is prepared as follows:

Crystal form A is treated with ethyl acetate of obtain Crystal form C. The Crystal form C is treated with a mixed solvent of ethyl acetate and water at a temperature of from 20°C to 40°C. The solvent is filtered and centrifuged to obtain Crystal form E. The resulting Crystal form E is suspended in a mixed solvent of ethyl acetate and water below 20°C, and Crystal form F is separated from the solvent by filtration, centrifugation or the like to yield a wet crystal.

The Crystal form F is dried under reduced pressure to obtain Crystal form D anhydrate. The Crystal form D anhydrate is conditioned to obtain Crystal form D hydrate. This is described in the specification as filed at page 8, line 6 to page 9, line 14.

The process for preparing the Crystal form D hydrate as claimed herein differs from the processes disclosed in the Miura patents in the following respects:

1. The crystal form from which the Crystal form D hydrate is prepared is different from the crystal form from which the Crystal form D is prepared.
2. The process for preparing the Crystal form D hydrate comprises steps of drying under reduced pressure and conditioning the Crystal form D anhydrate.

Koga discloses Crystal form A and a process for preparing the same in Example 57. Example 57 teaches that Crystal form A is obtained by recrystallizing Compound 6, which corresponds to a more specific compound, namely, a compound of formula (II) disclosed in the Miura patents, with a mixed solvent of methanol and isopropanol.

Since the treatment of Crystal form A as a starting material and subsequent plural treatment steps are required for obtaining the Crystal form D hydrate claimed herein, it is clear that the process for preparing the Crystal form D hydrate is quite different from the process for preparing Crystal form A.

Claim 4 is drawn to a process for preparing Crystal form D hydrate by conditioning Crystal form D anhydrate by storing Crystal form D anhydrate in a humidifying chamber, by spraying humidified vapor onto Crystal form D anhydrate, or the like. As stated above, none of Koga or the two Miura patents discloses this conditioning step. In addition, the Crystal form D hydrate as claimed herein has a novel crystalline structure. Thus, the process of claim 4 is not anticipated by any of Koga or the two Miura patents.

Furthermore, Crystal form D hydrate, which is superior in terms of stability and residual solvent, to the crystal forms described in Koga and the Miura patents, can be purified by the process of claim 4. Thus, it is clear that claim 4 is not obvious over any of Koga or the two Miura patents.

Claim 5 is directed to a process for preparing Crystal form D anhydrate by drying Crystal form F under reduced pressure. As stated above, none of Koga or the two

Miura patents discloses or suggests a step of drying under reduced pressure. In addition, the Crystal form F is a novel crystalline form. Thus, the process of claim 5 is novel and unobvious over any of Koga or the two Miura patents.

Additionally, Crystal form D anhydrate, which is an intermediate of the Crystal form D hydrate, can be prepared by the process of claim 5. This, it is clear that claim 5 is unobvious over any of Koga et al. and the two Miura patents in terms of part of the process for preparing the Crystal form D hydrate, which has been shown to be superior to the crystals of Koga and Miura patents in terms of stability and residual solvent.

Claim 6 is directed to a process for preparing Crystal form D hydrate from Crystal form F. As noted above, none of Koga nor the two Miura patents discloses the step of drying under reduced pressure or the step of conditioning. In addition, both the Crystal form F and the Crystal form D hydrate are novel substances. Thus, the process of claim 5 is novel over Koga or the two Miura patents.

In addition, Crystal form D hydrate is superior to the crystal forms described in Koga and the Miura patents in terms of stability and residual solvent. This Crystal form D hydrate is prepared by the process of claim 6. Therefore,

none of Koga or the two Miura patents can possibly anticipate the process of claim 6.

Claim 7 is directed to a process for preparing Crystal form D hydrate via Crystal form D anhydrate from Crystal form F. As stated above, none of Koga or the two Miura patents discloses a step of drying under reduced pressure or a step of conditioning. In addition, both the Crystal form F and the Crystal form D hydrate are novel substances. Thus, the process of claim 27 is novel over Koga or either of the two Miura patents.

Additionally, Crystal form D hydrate, which is superior in terms of stability and residual solvent to the crystal forms disclosed in Koga the two Miura patents, is prepared by the process of claim 7. Thus, the process of claim 7 cannot be obvious over Koga or either of the two Mira patents.

The crystal form of the compound recited in claim 8 is Crystal form G. Crystal form G is characterized by 2-theta angle positions in the powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°. None of Koga and the two Miura patents discloses any crystal that possess the same 2-theta angle position as crystal form G. Therefore, the crystal of claim 8 is novel over the crystal disclosed in Koga and the two Miura patents.

The crystal form of the compound recited in claim 10 is Crystal form G2. Crystal form G2 containing methylethylketone is characterized by 2-theta angle positions in its powder X-ray diffraction pattern of 5.4°, 10.4°, 10.7° and 12.1°. None of the cited patents discloses or suggests a crystal containing methylethylketone that possesses the same 2-theta angle position as Crystal form G2. Thus, the crystal form of claim 10 is novel over any of the cited patents.

Moreover, Crystal form G2 is useful as an intermediate for preparing Crystal form D hydrate. There is nothing in any of the cited patents that suggests this crystal form, or that it can be used to prepare Crystal form D hydrate.

The crystal form of the compound recited in claim 10 is Crystal form G3. Crystal form G3, containing tetrahydrofuran, is characterized by 2-theta angle positions in its powder X-ray diffraction pattern of 5.4°, 10.4° and 12.1°. None of the cited references discloses a crystal containing tetrahydrofuran that possesses the same 2-theta angle positions as Crystal form G3. Therefore, claim 11 is novel over Koga and either of the two Miura patents.

Additionally, Crystal form G3 can be used as an intermediate to prepare Crystal form D hydrate. None of Koga and the two Miura patents disclose or suggest this preparation.

The present amendment cancels claims 12-15, so the rejection of these claims is now moot.

Claim 16 is drawn to a process for preparing Crystal form D anhydrate from Crystal form G, Crystal form G1, Crystal form G2 or Crystal form G3. Each of these crystal forms is a novel crystal, and, therefore, none of the cited patents can be said to anticipate this compound.

Additionally, Crystal form D anhydrate, which is an intermediate of Crystal form D hydrate, which is superior in stability and residual solvent to the crystal forms described in the cited patents, can be obtained by the process of claim 16. Therefore, it is clear that none of Koga and the two Miura patents render claim 16 obvious.

Claim 17 is directed to a process for preparing Crystal form D hydrate from Crystal form G, Crystal form G1, Crystal form G2 or Crystal form G3. Each of these crystal forms is a novel crystal, and, therefore, none of the cited patents can be said to anticipate this compound.

Additionally, Crystal form D hydrate, which is superior in stability and residual solvent to the crystal forms described in Koga or the two Miura patents, can be prepared by the process of claim 17. Therefore, none of Koga or the two Miura patents renders claim 17 obvious.

Claim 18 is drawn to a process for preparing Crystal form D hydrate via Crystal form D anhydrate from Crystal form G, Crystal form G1, Crystal form G2 or Crystal form G3.


Each of these crystal forms is a novel crystal, and, therefore, none of the cited patents can be said to anticipate this compound or to render obvious this process.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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Amendments to the Abstract

Please delete the originally filed abstract of the disclosure and replace it with the attached replacement sheet.

Attachments: Replacement Sheet